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A Japanese familial case of myoclonus–dystonia syndrome with a splicing mutation in
the *SGCE* gene

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Running title:

A Japanese familial case of myoclonus–dystonia syndrome

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Abstract

Background Myoclonus–dystonia syndrome (MDS) is a rare autosomal-dominant movement disorder characterized by brief, frequently alcohol-responsive myoclonic jerks that begin in childhood or early adolescence, caused by mutations in the *SGCE* gene. **Case** The patient was a 6-year-old boy. At 2 years and 8 months, he presented with abnormal movement when he ran due to dystonia of his left leg. At 3 years and 5 months, he exhibited dystonia and myoclonic movement of his arms when he ate something. His myoclonus was likely to develop when he felt anxiety or exhaustion. His genomic DNA showed a heterozygous mutation in the *SGCE* gene [c.109+1 G>T]. His father and uncle with the same mutation also experienced milder dystonia or myoclonic movements. **Conclusion** *SGCE* mutation can cause a broad clinical spectrum inter- and intra-families. We should consider MDS as a differential diagnosis for patients with paroxysmal walking abnormalities and/or myoclonic movements.

Key words:

myoclonus–dystonia syndrome, ϵ -sarcoglycan, *SGCE* gene

Introduction

Syndromes presenting with dystonia can be divided into primary and secondary dystonia. Presently, 23 distinct monogenic primary dystonias (DYT1–25) have been recognized. DYT9 and DYT14 are now recognized as being identical to DYT18 and DYT5, respectively^{1, 2}. Clinically, these dystonias are categorized into 3 groups: (1) pure dystonia, in which dystonia is occasionally accompanied by tremor, (2) dystonia plus syndromes, in which dystonia as the prominent sign co-occurs with other movement abnormalities, such as myoclonus and parkinsonism and (3) dyskinesia (paroxysmal dystonia), in which dystonia occurs as a paroxysmal sign in association with other movement anomalies and sometimes seizures³. Early-onset dystonia comprised many heterogeneous diseases and is sometimes difficult to diagnose in clinical practice.

Myoclonus–dystonia syndrome (MDS; MIM #159900) is among dystonia plus syndromes, and a rare autosomal-dominant movement disorder characterized by brief, frequently alcohol-responsive myoclonic jerks that begin in childhood or early adolescence⁴. MDS is genetically heterogeneous because mutations in the ϵ -sarcoglycan

(*SGCE*) gene on 7q21 are identified only in 30–40% patients⁵, and the *SGCE* gene is maternally imprinted, and only the paternal allele is expressed. This is the report on a Japanese familial case of MDS with a splicing mutation in *SGCE*.

Case Report

A 6-year-old boy (Figure 1, III-2) was born to nonconsanguineous parents at 39 weeks and 3 days of gestational age, without asphyxia. At birth, his birth weight was 3235 g (+0.6 SD), height was 47.6 cm (-0.7 SD), occipito-frontal circumference was 36 cm (+1.9 SD). His motor development during infancy was slightly delayed: head control at 4 months, sitting alone at 6 months, standing and walking at 18 months. He started speaking complete words at 12 months. At 2 years and 8 months, the parents noticed that the boy's left leg became extended when he ran. At 3 years and 5 months, he exhibited abnormal movement of his right arm, but abnormal movement of his leg became unremarkable.

The patient was referred to our medical center because of his abnormal involuntary movement at 3 years and 8 months of age. His weight and height were 12.7

kg (−1.3 SD) and 84.4 cm (−3.7 SD), respectively. His neurological examination showed no particular neurological abnormalities including pyramidal or extrapyramidal signs, cerebellar ataxic signs, or asymmetric signs or symptoms.

His routine blood analysis was normal. Electroencephalography showed no abnormal discharges. Brain magnetic resonance imaging showed no abnormal lesions. His electrophysiological tests, including motor conducting velocity and muscle electrography, were not available.

His abnormal movements were as follows: when he tried to drink or eat something using his right hand, he could not control his arms, which either went too far to the left over his mouth or extended, and his head turned to the right or tilted to right, suggesting dystonia of the right arm and the left or right sternocleidomastoid, respectively. When he ate something with his left hand, his head turned to the right, suggesting dystonia of the left arm and left sternocleidomastoid. When he try to drink a cup of water with either his left or right hand, his arm sometimes exhibited fast movement, suggesting myoclonus, resulting in water spilling out of the cup. While running, his left leg seemed extended as though he was skipping. This occasionally

resulted in a forward fall, suggesting dystonia of the left leg. He independently presented with dystonia and myoclonus. His abnormal movement did not show diurnal fluctuation. Dystonia of his lower extremities became unrecognizable as he grew up. His myoclonus is likely to develop when he feels anxiety or exhaustion, or while he eats or writing letters. No clonazepam nor carbamazepine seemed effective for his myoclonic or dystonic movement. At present, he appears healthy, and although he occasionally displays abnormal movements, they do not interfere with his daily life.

His father (Figure 1, II-2) occasionally experienced stiffness in his hands during infancy, and sometimes has myoclonic movements of his arms when exhausted. His uncle (Figure 1, II-1) exhibited myoclonic movement of his arm during eating during his infancy and was diagnosed as having a tic. He also sometimes experienced myoclonic movements of his arms when exhausted. They did not consume alcohol and had no psychological problems.

To identify the mutation causing this family's autosomal-dominant dystonic syndrome, we performed whole-exome sequencing as described previously⁶. After written informed consent was provided, peripheral blood samples were obtained from

the patient (Figure 1, III-2), his father (Figure 1, II-2) and mother (Figure 1, II-3), his brother (Figure 1, III-1), his uncle (Figure 1, II-1), his paternal grandfather (Figure 1, I-1), and his grandmother (Figure 1, I-2). We detected a heterozygous mutation consisting of a nucleotide change in the consensus sequence for the splice donor site in intron 1 in the *SGCE* gene [c.109+1 G>T] in three symptomatic family members, including the patient, his father, his uncle and his apparently asymptomatic grandfather (I-1). The mutation was not found in the asymptomatic family members, including his mother, brother and grandmother (I-2). This mutation is expected to be pathogenic, because it has been already reported in a large family with MDS⁷, and the mutation was shown to cause an abnormal splicing.

Discussion

We identified on a known splicing mutation of *SGCE* in a family with MDS, and detailed clinical symptoms and neurological features of the proband were reported. Our case is characteristic in that he presented with an initial symptom of one-sided leg dystonia only while running at 2 years and 8 months old. In a recent study on nine MSD

patients under 18 years old, *SGCE* mutations were identified in seven patients⁸. In most of these patients, dystonia simultaneously appeared with myoclonus, or later than myoclonus, with onset occurring from 8 months to 9 years in 8 out of 9 patients.

The family described in this report showed the same splicing mutation with the patient reported previously, exhibiting a unique phenotype mimicking moyamoya disease⁷. None of the patient's family members presented with moyamoya disease, suggesting that this splicing mutation is unlikely to be involved in the onset of moyamoya disease. Additionally, None of our families were heavy drinkers, and had any psychiatric disorders like those patients. It has been suggested that excess alcohol consumption in MDS could be a consequence of primary disorder of compulsive behavior, rather than the result of a therapeutic effect of alcohol on myoclonus⁹. Careful observation of the present family suggests that this *SGCE* mutation is not necessarily cause psychiatric features as reported previously, and that there is a broad clinical spectrum inter- and intra-families.

The patient's grandfather (Figure 1, I-1), who carried the mutation, showed no apparent signs and symptoms. This may be because his mutated allele was inherited

from his mother and, since *SGCE* is maternally imprinted, the mutated maternal allele is not transcribed and the normal paternal allele is expressed, although this was not confirmed. This imperfect penetrance may make sometimes diagnosis difficult.

In the previous report, trihexyphenidyl and clonazepam seemed more useful than carbamazepine, levetiracetam, valproate, or gabapentin. Deep brain stimulation of the globus pallidus pars interna seems effective in some adults and children with MDS. Spontaneous remission of dystonia and myoclonus may occur in approximately 20% and 5% patients with MDS during childhood or adolescence, respectively¹⁰. As observed in our patients, some patients can grow out of dystonia and myoclonus without any treatment, and we have to carefully consider the choice and timing of treatment¹¹.

We should consider MDS as a differential diagnosis for infants with paroxysmal abnormal movements of arms or legs.

Conflict of interest statement

We have no conflict of interest to disclose.

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Figure Legend

Figure 1; A family tree of the present family and the electrophoregrams of the Sanger sequencing of SGCE.

Details are described in the text.

WT: wild allele

Figure 1

